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Letter to the Editor

Antibody titers and protection against a SARS-CoV-2 infection

Dear editor,

Recent studies indicate that binding and neutralizing SARS-CoV-2 antibodies elicited by natural infection or vaccination persist for more than 6 months although their concentration decreases over time.¹ The passive transfer of neutralizing antibodies (NAb) and protection are correlated in non-human primates.² While such a link has not yet been defined in humans, individuals with a high NAb titer could well be better protected against SARS-CoV-2. A recent letter in Journal of Infection indicated that indeed neutralizing antibodies are considered linked to protective immunity due to their ability to block the viruses from entering the host cells. The authors discussed the decrease in neutralizing antibodies after vaccination without being able to provide a threshold below which protection against SARS-CoV-2 infection is no longer guaranteed.³

We measured the antibody titers in 8758 healthcare workers (HCWs), vaccinated and unvaccinated, soon after the first epidemic wave had occurred in France (10 June–10 July, 2020). Total SARS-CoV-2 antibodies were measured in longitudinal samples

with a quantitative enzyme-linked immunosorbent assay (ELISA) (Wantai Biological Pharmacy Enterprise Co., Ltd, China) and a live-virus neutralization assay using Vero cells and a B.1.160 strain (GI-SAID EPI-ISL-804372).⁴ Symptomatic and asymptomatic infections were detected with a nucleic-acid amplification method (AptimaTM SARS-CoV-2 assay, PantherTM system, Hologic, USA).⁵ This study was approved by the French Research Ethics Committee Est-III (COVID BioToul, ID-RCB 2020-A01292-37, ClinicalTrials.gov Identifier: NCT04385108).

The median age of the 8758 HCWs (7039; 80.4% females) was 40 years (interquartile range [IQR] 32–50). Over half of them (4811; 54.9%) had been given one (2244; 46.6%) or two (2567; 53.4%) doses of vaccine between January and April 15, 2021. Of these, 1290 (26.8%) had one dose of the Oxford–AstraZeneca ChAdOx1 nCoV-19 (AZD1222) vaccine, 954 (19.8%) had one dose of the Pfizer–BioNTech COVID-19 mRNA (BNT162b2) vaccine and 2567 (53.4%) had two doses. An average of 9.65% (range [7.2–12.1%]) of the HCW who had no NABs became infected after a median follow-up of 275 days (IQR: 265–281), as did 2.2% [95% CI: 0.4–4%] of those with a NAB titer well below 64. In contrast only 0.6% [95% CI: 0–1.5%] of those with NAB titers of 64 to 128 became infected to-

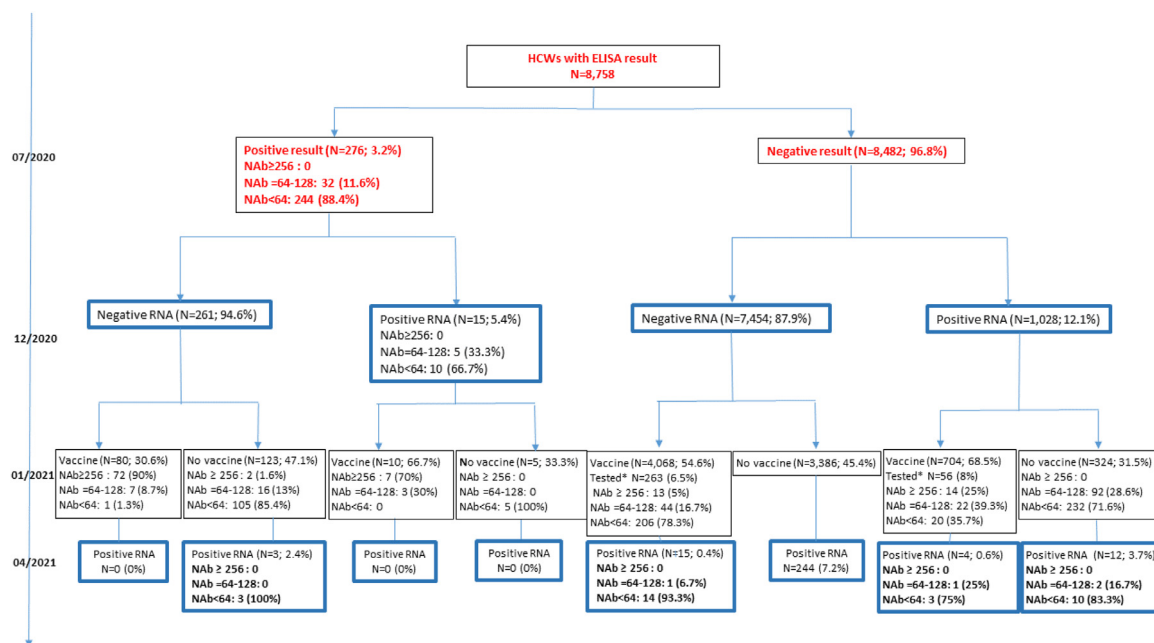


Fig. 1. Study flowchart. The NAB titers were obtained at each time of ELISA screening (July 2020, January 2021) for all ELISA-positive samples. The January 2021 NAB titers for vaccinated HCWs were obtained three weeks after administration of the first or second vaccine dose. Finally, the NAB titers reported for December 2020 and April 2021 were those obtained at the previous screening (July 2020 and January 2021, respectively) and for which an infection occurred during the following three months.

*Representative sample based on age and gender

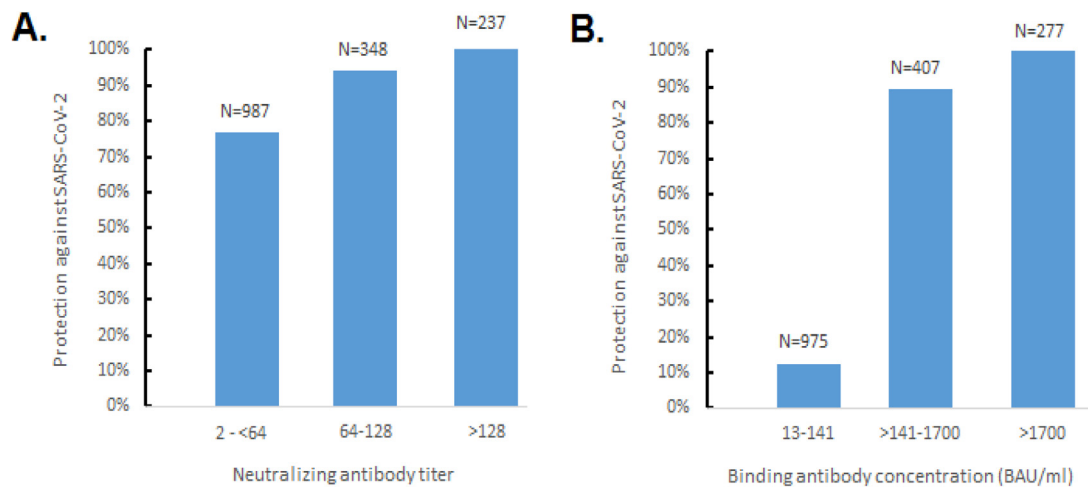


Fig. 2.. Protection against SARS-CoV-2 according to neutralizing (A) or binding (B) antibody classes.

gether with none of those with NAb titers of 256 and above (Fig. 1, $p < 0.01$, Chi² test). The correlation between the ELISA total antibody values expressed in binding antibody units (BAU) per ml using the WHO international standard (NIBSC code 20/136)⁶ and the neutralizing antibody titers from July 2020 to April 2021 was 0.8 for unvaccinated HCWs and 0.79 for vaccinated HCWs. Analysis of ELISA total antibody concentrations indicated that 12.1% [95% CI: 11.5–12.8%] of HCWs with a negative ELISA or an ELISA concentration below 13 BAU/ml became infected between July 2020 and April 2021, as did 10.6% [95% CI: 6.5–16.1%] of HCWs that had an ELISA concentration between 13 and 141 BAU/ml. In contrast only 1.3% [95% CI: 0.03–7.2%] of those with an ELISA concentration between 141 and 1700 BAU/ml became infected and none of those with an ELISA concentration of 1700 BAU/ml and above ($p < 0.01$, Chi² test). Analysis of all the data indicated that a NAb titer well below 64 provided 76.8% protection against SARS-CoV-2, a titer of 64 to 128 gave 94% protection and a NAb titer of 256 or more provided full (100%) protection (Fig. 2A). In the same way, an ELISA concentration between 13 and 141 BAU/ml provided only 12.4% protection against SARS-CoV-2, a concentration between 141 and 1700 BAU/ml provided 89.3% protection and a concentration of 1700 BAU/ml and above provided full protection (Fig. 2B). In our cohort, none of the two doses-vaccinated HCWs had an ELISA concentration below 141 BAU/ml one month after the second injection, unlike 79.3% of the HCWs three months after a natural infection.

Our study did not assess cell-mediated immunity and all the subjects were HCWs. However, the data suggest that monitoring the neutralizing antibody response but also total antibody concentrations, logistically more feasible, can be used to optimize vaccination strategies by estimating the duration and degree of protection provided by vaccines. The thresholds of protection found in our study should be compared to those obtained in further studies on other populations. It is also essential to estimate the influence of an antibody's reduced neutralizing capacity against new emerging viruses variants [7,8].

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Declaration of Competing Interest

The authors declare no conflict of interest

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References

- Doria-Rose N, Suthar MS, Makowski M, O'Connell S, McDermott AB, Flach B, et al. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for COVID-19. *N Engl J Med* 2021; **384**(23):2259–61. doi:10.1056/NEJMc2103916.
- McMahan K, Yu J, Mercado NB, Loos C, Tostanoski LH, Chandrashekar A, et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. *Nature* 2021; **590**(7847):630–4. doi:10.1038/s41586-020-03041-6.
- Douxflis J, Gillot C, Mullier F, Favresse J. Post-SARS-CoV-2 vaccination specific antibody decrease - thresholds for determining seroprevalence and seroneutralization differ. [published online ahead of print]. *J Infect* 2021; **S0163-4453**(21):00405–9. doi:10.1016/j.jinf.2021.08.023.
- Dimeglio C, Herin F, Miedougé M, Cambus JP, Abravanel F, Mansuy JM, et al. Screening for SARS-CoV-2 antibodies among healthcare workers in a university hospital in southern France. *J Infect* 2020; **82**(1):e29–e32. doi:10.1016/j.jinf.2020.09.035.
- Trémeaux P, Lhomme S, Abravanel F, Raymond S, Mengelle C, Mansuy JM, et al. Evaluation of the AptimaTM transcription-mediated amplification assay (Hologic[®]) for detecting SARS-CoV-2 in clinical specimens. *J Clin Virol* 2020; **129**:104541. doi:10.1016/j.jcv.2020.104541.
- Kumar A, Bernasconi V, Manak M, de Almeida Aranha AP, Kristiansen PA. The CEPI centralised laboratory network: supporting COVID-19 vaccine development. *Lancet* 2021; **397**(10290):2148–9. doi:10.1016/S0140-6736(21)00982-X.
- Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant delta to antibody neutralization. *Nature* 2021; **596**(7871):276–80. doi:10.1038/s41586-021-03777-9.
- Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, et al. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. *Lancet* 2021; **397**(10292):2331–3. doi:10.1016/S0140-6736(21)01290-3.

Chloé Dimeglio*

Virology Laboratory, Toulouse University Hospital, 330 avenue de Grande Bretagne 31059, Toulouse 31300 France
INSERM UMR 1291 – CNRS UMR 5051, Toulouse Institute for Infectious and Inflammatory Diseases (INFINITY), Toulouse 31300, France

Fabrice Herin

Occupational Diseases Department, Toulouse University Hospital, Toulouse 31000, France
UMR1295, unité mixte INSERM, Université Toulouse III Paul Sabatier, Centre for Epidemiology and Research in Population Health Unit (CERPOP), Toulouse 31000, France

Guillaume Martin-Blondel

*INSERM UMR 1291 – CNRS UMR 5051, Toulouse Institute for
Infectious and Inflammatory Diseases (INFINITY), Toulouse 31300,
France
Infectious and Tropical Diseases Department, Toulouse University
Hospital, Toulouse 31300, France*

Marcel Miedougé

*Virology Laboratory, Toulouse University Hospital, 330 avenue de
Grande Bretagne 31059, Toulouse 31300 France*

Jacques Izopet

*Virology Laboratory, Toulouse University Hospital, 330 avenue de
Grande Bretagne 31059, Toulouse 31300 France
INSERM UMR 1291 – CNRS UMR 5051, Toulouse Institute for
Infectious and Inflammatory Diseases (INFINITY), Toulouse 31300,
France*

*Corresponding author at: Virology Laboratory, Toulouse
University Hospital, 330 avenue de Grande Bretagne 31059,
Toulouse 31300 France.

E-mail address: dimeglio.c@chu-toulouse.fr (C. Dimeglio)